



**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of: Mattheakis et al.

Attorney Docket No.: CYTOP135X1

Application No.: 10/719,988

Examiner: UNASSIGNED

Filed: November 20, 2003

Group: 1645

Title: PREDICTING HEPATOTOXICITY USING  
CELL BASED ASSAYS

**CERTIFICATE OF MAILING**

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as first-class mail on March 29, 2004 in an envelope addressed to the Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313-1450.

Signed: \_\_\_\_\_

Leslie Russell

**INFORMATION DISCLOSURE STATEMENT  
37 CFR §§1.56 AND 1.97(b)**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

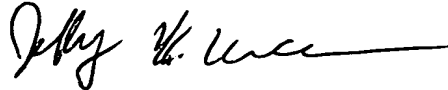
The references listed in the attached PTO Form 1449 may be material to examination of the above-identified patent application. Applicants submit the list of these references in compliance with their duty of disclosure pursuant to 37 CFR §§1.56 and 1.97. The Examiner is requested to make these references of official record in this application. The above-identified application is a Continuation-in-Part of prior application U.S. Patent Application No. 10/623,486. This prior application is being relied upon for an earlier filing date under 35 U.S.C. § 120. Because the listed references were either cited by the PTO, or submitted to the PTO in the prior application, under 37 CFR § 1.98(d) Applicants submit that copies need not be provided.

This Information Disclosure Statement is not to be construed as a representation that a search has been made, that additional information material to the examination of this application does not exist, or that these references indeed constitute prior art.

This Information Disclosure Statement is: (i) filed within three (3) months of the filing date of the above-referenced application, (ii) believed to be filed before the mailing date of a first Office Action on the merits, or (iii) believed to be filed before the mailing of a first Office Action after the filing of a Request for Continued Examination under §1.114. Accordingly, it is believed that no fees are due in connection with the filing of this Information Disclosure

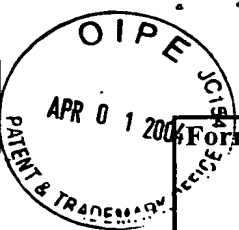
Statement. However, if it is determined that any fees are due, the Commissioner is hereby authorized to charge such fees to Deposit Account 500388 (Order No. CYTOP135X1).

Respectfully submitted,  
BEYER WEAVER & THOMAS, LLP

A handwritten signature in black ink, appearing to read "Jeffrey K. Weaver", with a long horizontal flourish extending to the right.

Jeffrey K. Weaver  
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<b>Form 1449 (Modified)</b>  <b>Information Disclosure Statement By Applicant</b>  (Use Several Sheets if Necessary)	<table style="width: 100%;"> <tr> <td style="width: 50%;">           Atty Docket No. CYTOP135X1 Applicant: Mattheakis et al. Filing Date November 20, 2003         </td> <td style="width: 50%;">           Application No.: 10/719,988  Group 1645         </td> </tr> </table>	Atty Docket No. CYTOP135X1 Applicant: Mattheakis et al. Filing Date November 20, 2003	Application No.: 10/719,988  Group 1645
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**U.S. Patent Documents**

Examiner Initial	No.	Patent No.	Date	Patentee	Class	Sub- class	Filing Date
	A1	4,818,710	04/04/89	Sutherland et al.			
	A2	4,922,092	05/01/90	Rushbrooke et al.			
	A3	4,959,301	09/25/90	Weaver et al.			
	A4	4,965,725	10/23/90	Ruttenberg			
	A5	5,287,272	02/15/94	Rubbenberg et al.			
	A6	5,326,691	07/05/94	Hozier			
	A7	5,355,215	10/11/94	Schroeder et al.			
	A8	5,526,258	06/11/96	Bacus			
	A9	5,548,661	08/20/98	Price et al.			
	A10	5,655,028	08/05/97	Soll et al.			
	A11	5,733,721	03/31/98	Hemstreet III et al.			
	A12	5,741,648	04/21/98	Hemstreet III et al.			
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	A15	5,790,710	08/04/98	Price et al.			
	A16	5,804,436	09/08/98	Okun et al.			
	A17	5,856,665	01/05/99	Price et al.			
	A18	5,893,095	04/06/99	Jain et al.			
	A19	5,919,646	07/06/99	Okun et al.			
	A20	5,932,872	08/03/99	Price			
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	A22	5,976,825	11/02/99	Hochman			
	A23	5,989,835	11/23/99	Dunlay et al.			
	A24	5,991,028	11/23/99	Cabib et al.			
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	A29	6,103,479	08/15/00	Taylor			
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	A32	6,345,115	02/05/02	Ramm et al.			
	A33	5,162,990	11/10/92	Odeyale et al.			
	A34	RE 34,214	04/06/93	Carlsson et al.			
Examiner				Date Considered			

Examiner: Initial citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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	November 20, 2003	1645

#### U.S. Patent Documents

Examiner Initial	No.	Patent No.	Date	Patentee	Class	Sub-class	Filing Date
	A35	6,599,694	07/29/03	Elias			

#### Foreign Patent or Published Foreign Patent Application

Examiner Initial	No.	Document No.	Publication Date	Country or Patent Office	Class	Sub-class	Translation	
							Yes	No
	B1	WO00/50872	08.31.00	WIPO				
	B2	WO00/33250	06.08.00	WIPO				
	B3	WO00/49540	08.24.00	WIPO				
	B4	WO00/43820	07.27.00	WIPO				
	B5	WO00/03246	01.20.00	WIPO				
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	B7	WO99/05323	02.04.99	WIPO				
	B8	WO99/08091	02.18.99	WIPO				
	B9	WO99/17116	04.08.99	WIPO				
	B10	WO00/17643	03.30.00	WIPO				
	B11	WO 95/10036	13.04.05	WIPO				
	B12	WO 98/44333	08.10.98	WIPO				
	B13	WO 00/17624	30.03.00	WIPO				
	B14	WO 00/17808	30.03.00	WIPO				
	B15	WO 93/21511	28.10.93	WIPO				
	B16	WO 94/11841	26.05.94	WIPO				
	B17	WO 95/22749	24.08.95	WIPO				
	B18	WO 96/01438	18.01.96	WIPO				
	B19	WO 96/09605	28.03.96	WIPO				
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	B23	WO 97/45730	04.12.97	WIPO				
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	B25	WO 98/35256	13.08.98	WIPO				
	B26	WO 98/38490	03.09.98	WIPO				
	B27	WO 00/06774	10.02.00	WIPO				
	B28	WO 00/26408	11.05.00	WIPO				
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	B30	WO 00/70528	23.11.00	WIPO				
	B31	WO 00/60356	12.10.00	WIPO				
	B32	WO 00/29984	25.05.00	WIPO				
	B33	WO 87/02802	07.05.87	WIPO				
	B34	WO 99/44062	02.09.99	WIPO				
	B35	WO 99/54494	28.10.99	WIPO				
	B36	WO 99/67739	29.12.99	WIPO				
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	B38	WO 98/52018	19.11.98	WIPO				
	B39	0 317 139 B1	02.11.95	European				
	B40	0 468 705 A2	29.01.92	European				
	B41	EP 0 902 394 A1	17.03.99	European				

**Other Documents**

Examiner Initial	No.	Author, Title, Date, Place (e.g. Journal) of Publication
	C1	Kapur <i>et al.</i> , "Design and Fabrication of Spatially Controlled Miniaturized Organ Systems from Stem Cells", US provisional application serial number 60/127,339, filed April 1, 1999
	C2	Adams <i>et al.</i> , "Cell Patterning on Glass and Polymeric Substrates", US Provisional application serial number 60/138,119, filed June 7, 1999
	C3	Dunlay <i>et al.</i> , "Data Management and Presentation Methods", US Provisional application serial number 60/140,240, filed June 21, 1999
	C4	Blankenstein <i>et al.</i> , "Modular concept of a laboratory on a chip for chemical and biochemical analysis, © 1998, Biosensors & Bioelectronics, Vol. 13., No. 3-4, pp. 427-438.
	C5	István Cseke, "A Fast Segmentation Scheme for White Blood Cell Images", © 1992 IEEE, pp. 530-533.
	C6	Hofland <i>et al.</i> , "Role of Tumor-Derived Fibroblasts in the Growth of Primary Cultures of Human Breast-Cancer Cells: Effects of Epidermal Growth Factor and the Somatostatin Analogue Octreotide", © 1995 Wiley-Liss, Inc., Publication of the International Union Against Cancer, pp. 93-99.
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**Other Documents**

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	C7	Boyce <i>et al.</i> , "Systems and Methods to Achieve Integrated Presentation of Summary Statistics, Detail Measurements, and Raw Images While Maintaining Efficient Use of Storage Media Through Separation of the Data in an Integrated Data Management and Presentation System", US provisional application serial number 60/108,291, filed November 13, 1998
	C8	Boyce <i>et al.</i> , "Data Management and Presentation Methods", US Provisional application serial number 60/142,375, filed July 6, 1999
	C9	Boyce <i>et al.</i> , "Data Management and Presentation Methods", US Provisional application serial number 60/142,646, filed July 6, 1999
	C10	Roger James, "A Pulsed Polarimeter", US Provisional application serial Number 60/110,643, filed December 1, 1998
	C11	Wang <i>et al.</i> , "Database for Storage, Retrieval, and Analysis of Cellular Information", US Provisional application serial number 60/120,801, filed February 19, 1999
	C12	Printout from Q3DM Website ( <a href="http://www.Q3DM.com">www.Q3DM.com</a> ), printed on March 1, 2001, 30 pages.
	C13	Printout from Automated Cell Website ( <a href="http://www.automatedcell.com">www.automatedcell.com</a> ), printed on March 9, 2001, 24 pages.
	C14	Pauwels, et al., "Determination of the Mechanism of Action of Anticancer Drugs by Means of the Computer-Assisted Microscope Image Analysis of Feulgen-Stained Nuclei", J. Pharmacological and Toxicological Methods, 37: 105-115 (1997).
	C15	Pauwels, et al., "Monitoring of chemotherapy-induced morphonuclear modifications by means of digital cell-image analysis", I. Cancer Res. Clin. Oncol., 119: 533-540 (1993).
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	C17	Pauwels, et al., "The Application of Computerized Analysis of Nuclear Images and Multivariate Analysis to the Understanding of the Effects of Antineoplastic Agents and Their Mechanism of Action", Meth. Find. Exp. Clin Pharmacol, 15(2): 113-124 (1993).
	C18	Pauwels, et al., "Combination of Computerized Morphonuclear and Multivariate Analysis to Characterize In Vitro the Antineoplastic Effect of Alkylating Agents", J. Pharmacol. and Toxicol. Methods, 33(1): 34-45 (1995).
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	C20	Sundblad, et al., "The use of image analysis and automation for measuring mitotic index in apical conifer meristems", October 1998, Journal of Experimental Botany, Vol. 49, No. 327, pp. 1749-1756.
	C21	Takayama et al., "Patterning cells and their environments using multiple laminar fluid flows in capillary networks", (1999) Proc. Natl., Acad. Sci USA, 96:5545-5548.
	C22	Weinstein, et al., "An Information-Intensive Approach to the Molecular Pharmacology of Cancer", Science, 275: 343-349 (January 17, 1997).
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	C24	Ng et al., "Evaluating Multi-Dimensional Indexing Structures for Images Transformed by Principal Component Analysis", Proceedings of SPIE, Bellingham, Spie, US (1996), Vol. 2670, pp. 50-61.
	C25	Boland et al., "Automated Recognition of Patterns Characteristic of Subcellular Structures in Fluorescence Microscopy Images", Rapid Communications, Cytometry 33:366-375 (1998).
	C26	Giuliano <i>et al.</i> , "High-Content Screening: A New Approach to Easing Key Bottlenecks in the Drug Discovery Process", © 1997 The Society for Biomolecular Screening, Inc., Journal of Biomolecular Screening, Vol. 2, No. 4, 1997, pp. 249-258.
	C27	Montironi <i>et al.</i> "Computed cell cycle and DNA histogram analyses in image cytometry in breast cancer", 1993, pp.795-800.
	C28	Giuliano <i>et al.</i> , "Fluorescent-protein biosensors: new tools for drug discovery", March 1998, Vol. 16, pp.135-140.
	C29	Kobayashi N, et al., "Prevention of acute liver failure in rats with reversibly immortalized human hepatocytes", Science, Vol. 287, February 18, 2000, 1258-1262.
	C30	Lieber, C.S., "Alcohol and liver: metabolism of alcohol and its role in hepatic and extrahepatic diseases, The Mount Sinai Journal of Medicine", Vol. 67, No. 1, January 2000, pp. 84-94.
	C31	Baroana, E., et al., "Alcoholic hepatomegaly: accumulation of protein in the liver", Science, Vol. 190, 1975, pp. 794-5.
	C32	Tuchweber, B. et al., "Mechanisms Of Experimentally Induced Intrahepatic Cholestasis", Progress in Liver Diseases, (1986), pp. 161-178.
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**Other Documents**

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	C33	McMillian, et al., "Nile Red Binding to HepG2 Cells: An Improved Assay for In Vitro Studies of Hepatosteatosi", In Vitro & Molecular Toxicology, Volume 14, Number 3, 2001, pp. 177-190.
	C34	Watanabe, S. et al., "Phalloidin Alters Bile Canalicular Contractility In Primary Monolayer Cultures Of Rat Liver", Gastroenterology, (1983), 85, pp.245-253.
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	C37	Greenspan, P., et al., "Nile Red: A Selective Fluorescent Stain For Intracellular Lipid Droplets," J Cell Biol, 1985, Vol. 100, No. 3, pp. 965-973.
	C38	Amacher, D.E., "A toxicologist's guide to biomarkers of hepatic response", Hum Exp Toxicol, 2002, 21(5): p. 253-262.
	C39	Amacher, D.E., et al., "Tetracycline-Induced Steatosis In Primary Canine Hepatocyte Cultures," Fundam Appl Toxicol, 1997, 40(2): p. 256-263.
	C40	Kutsyy et al., "Methods and Apparatus for Investigating Side Effects", U.S. Patent Application No. 10/621,821, (Atty. Docket CYTOP110), filed July 16, 2003.
	C41	Vaisberg et al., "Characterizing Biological Stimuli By Response Curves", U.S. Patent Application No. 09/789,595, (Atty. Docket CYTOP011), filed February 20, 2001.
	C42	Crompton et al., "A Database Method for a Predictive Cellular Bioninformatics," U.S. Patent Application No. 09/310,879 (Atty. Docket CYTOP006), filed on May 14, 1999.
	C43	Crompton et al., "Database System Including Computer For Predictive Cellular Bioninformatics," U.S. Patent Application No. 09/311,996, (Atty. Docket CYTOP007), entitled filed on May 14, 1999.
	C44	Crompton et al., "A Database System For Predictive Cellular Bioninformatics," U.S. Patent Application No. 09/311,890 (Atty. Docket CYTOP008), filed on May 14, 1999.
	C45	Vaisberg, et al., "Image Analysis Of The Golgi Complex", U.S. Patent Application No. 09/792,012, (Atty. Docket CYTOP012), filed on February 20, 2001.
	C46	Coleman et al., "Methods and Apparatus For Characterising Cells And Treatments", US Patent Application No. 10/615,116, (Atty. Docket CYTOP111), filed July 7, 2003.
	C47	Cong et al., "Extracting Shape Information Contained In Cell Images", U.S. Patent Application No. 09/792,013, (Atty. Docket CYTOP013), filed February 20, 2001.
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	C48	Serbouti, et al., "Image Segmentation and Classification Methods to Detect Leukemias", (1991) Annual Int'l Conf. of IEEE Eng. In Medicine & Biology Soc., Vol. 13, No. 1, pp. 0260-0261.
	C49	Vaisberg et al., "Classifying Cells Based on Information Contained In Cell Images", U.S. Application No. 09/729,754, (Atty. Docket CYTOP005), filed December 4, 2000.
	C50	Vaisberg, et al., "Characterizing Biological Stimuli By Response Curves," U.S. Patent Application No. 09/789,595, (Atty. Docket CYTOP140), filed February 20, 2001.
	C51	Rubas et al., "An Integrated Method to Determine Epithelial Transport and Bioactivity of Oral Drug Candidates in Vitro", Rapid Communication, Pharmaceutical Research, Vol. 13, No. 1, 1996, pp. 23-26.
	C52	Nilsson, et al., "Segmentation of Dense Leukocyte Clusters", IEEE Workshop on Mathematical Methods in Biomedical Image Analysis, 2001, pp. 221-227.
	C53	Malpica et al., "Applying Watershed Algorithms to the Segmentation of Clustered Nuclei", Cytometry, Vol. 28, 1997, pp. 289-297.
	C54	Ancin, et al., "Advances in Automated 3-D Image Analysis of Cell Populations Imaged by Confocal Microscopy", Cytometry, Vol. 25, 1996, pp. 221-234.
	C55	Blom, et al., "Regional loss of the mitochondrial membrane potential in the hepatocyte is rapidly followed by externalization of phosphatidyl serines at that specific site during apoptosis", JBC Papers in Press, published on January 21, 2003, pp. 1-36.
	C56	Uria, et al., "Regulation of Collagenase-3 Expression in Human Breast Carinomas Is Mediated by Stromal-Epithelial Cell Interactions", Cancer Research 57, November 1, 1997, pp. 4882-4888.
	C57	Zimmerman, H.J., "Expressions of Hepatotoxicity", Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver, Section I, General Considerations, 2 <sup>nd</sup> Edition, 1999, pp. 61-109.
	C58	Zimmerman, H.J., "Classification of Hepatotoxins and Mechanisms of Toxicity", Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver, Section I, General Considerations, 2 <sup>nd</sup> Edition, 1999, pp. 111-145.
	C59	Zimmerman, H.J., "Experimental Hepatotoxicity", Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver, Section II, General Considerations, 2 <sup>nd</sup> Edition, 1999, pp. 201-228.
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	C60	Zimmerman, H.J., "Toxic Cholestasis", Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver, Section II, General Considerations, 2 <sup>nd</sup> Edition, 1999, pp. 295-323.
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